Poster 195

Phase 3 Topline Results of DT120 (Lysergide) in Generalized Anxiety Disorder

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Background

- Generalized anxiety disorder (GAD) is a chronic condition characterized by excessive worry and anxiety.[1] GAD is among the most prevalent psychiatric conditions, affecting approximately 10% of adults in the United States and 4% of adults globally[2–4]
- Although there are several treatments for GAD, it is estimated that 50% of patients do not respond to first-line therapies, which often take several weeks to produce clinical effects and can be accompanied by side effects[5,6]
- There is a significant need to identify novel treatment strategies for GAD
- DT120 orally disintegrating tablet (ODT) is an ergoline derivative belonging to the group of classic serotonergic psychedelics, which acts as a partial agonist at serotonin-2A (5-HT2A) receptors. DT120 ODT is currently under development for the treatment of GAD
- Results from a previous phase 2b study evaluating the safety and efficacy of DT120 in adults with GAD demonstrated that a single 100-µg dose of DT120 was well tolerated and led to clinically meaningful reductions in GAD symptoms[7]

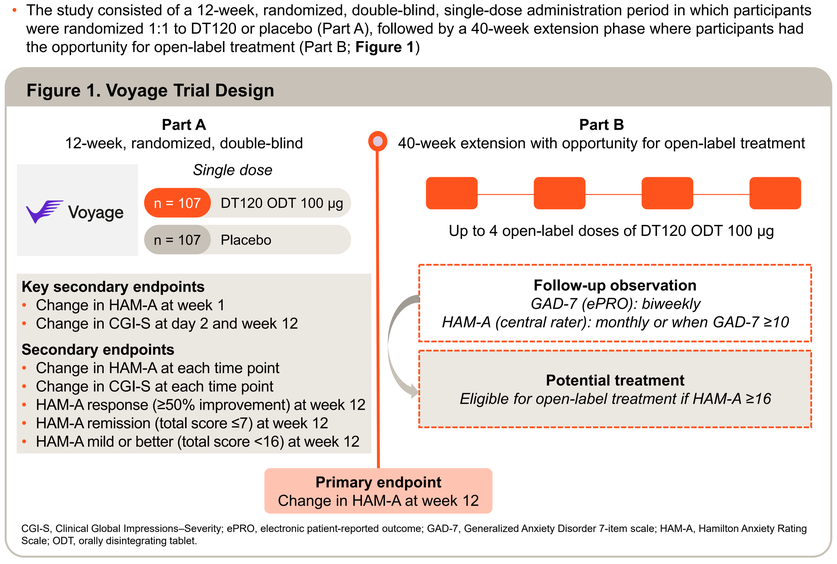
Objective

- To report topline efficacy and safety results from Voyage (NCT06741228), a phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluating a single 100-µg dose of DT120 in adults with GAD

Methods

- The study enrolled 214 participants aged 18 to 74 years with a primary diagnosis of GAD who had a minimum Hamilton Anxiety Rating Scale (HAM-A) total score of ≥20 at screening and baseline
- Participants were excluded if they had medical or psychiatric conditions that were contraindicated, or if they were taking concomitant medications, supplements, or other therapeutics with potential drug–drug interactions or anxiolytic or antidepressant effects that could not be discontinued
- The study consisted of a 12-week, randomized, double-blind, single-dose administration period in which participants were randomized 1:1 to DT120 or placebo (Part A), followed by a 40-week extension phase where participants had the opportunity for open-label treatment (Part B; **Figure 1**)

Figure 1. Voyage Trial Design



CGI-S, Clinical Global Impressions–Severity; ePRO, electronic patient-reported outcome; GAD-7, Generalized Anxiety Disorder 7-item scale; HAM-A, Hamilton Anxiety Rating Scale; ODT, orally disintegrating tablet.

Results

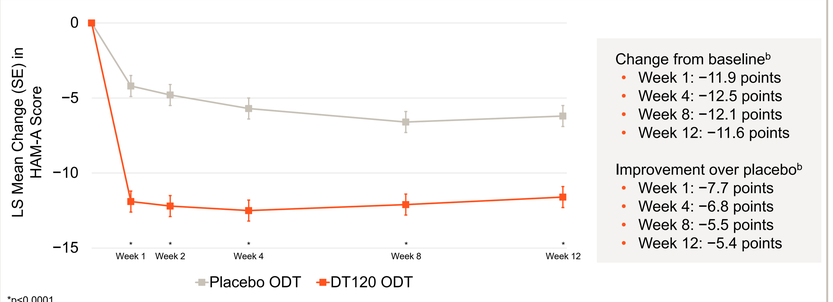
- A total of 845 participants were screened for eligibility. Of these, 214 participants were randomized 1:1 to receive a single administration of 100 µg of DT120 (n = 107) or placebo (n = 107; **Table 1**)
- DT120 met the primary endpoint, demonstrating a significant 11.6-point improvement in HAM-A from baseline to week 12 (p<0.0001)
- Significant improvements were observed as early as week 1 and were maintained through week 12, with a 5.4-point placebo-adjusted improvement at the end of the double-blind period (p<0.0001; **Figure 2**)
- Key secondary endpoints were met with an 11.9-point improvement in HAM-A from baseline at week 1 (p<0.0001) and a 1.0-point improvement in Clinical Global Impressions–Severity (CGI-S) score at day 2 and week 12 (p<0.0001). Secondary endpoints were also met, including significant improvements in CGI-S scores at all time points (**Figure 3**)
- Participants who received DT120 demonstrated significantly higher response and remission rates at week 12 compared with those who received placebo, supporting the clinical relevance of the observed effects (**Figure 4**)
- The treatment effect was maintained across key subgroups, including in participants with ≥2 previous trials of medications for GAD (**Figure 5**)
- DT120 was generally well tolerated. No serious adverse events (AEs), suicidal behavior, or self-injurious behavior were reported during Part A of the study
- The AE profile was consistent with prior studies of DT120.[6] All AEs reported for DT120 ODT were mild to moderate in severity (**Table 2**). The most common treatment-emergent AEs (TEAEs) were illusion, nausea, and euphoric mood. The majority of TEAEs occurred on the dosing day. The most common TEAE reported after the dosing day was headache
- Average time to End-of-Session Checklist (EoSC) clearance was 6.4 hours (**Figure 6**). More than half of participants met all EoSC criteria at hour 6, and the majority of participants (90%) met all EoSC criteria by hour 8

Table 1. Demographics and Baseline Characteristics[a]

Participant characteristics	DT120 ODT n = 107	Placebo ODT n = 107	Overall N = 214
Age, mean (range), years	42 (21–72)	43 (20–67)	42 (20–72)
Sex, n (%)			
Female	63 (59)	74 (69)	137 (64)
Male	44 (41)	33 (31)	77 (36)
Race, n (%)			
American Indian or Alaska Native	3 (3)	0	3 (1)
Asian	8 (7)	9 (8)	17 (8)
Black or African American	9 (8)	19 (18)	28 (13)
Native Hawaiian or Other Pacific Islander	0	0	0
White	78 (73)	77 (72)	155 (72)
Not reported	4 (4)	1 (1)	5 (2)
Unknown	1.0 (0.9)	0	1.0 (0.5)
Multiple	4 (4)	1 (1)	5 (2)
Baseline HAM-A score, mean (SD)[b]	28.4 (5.9)	27.4 (5.5)	27.9 (5.7)
GAD severity based on HAM-A score, n (%)			
Moderate (<24)[c]	26 (24)	28 (26)	54 (25)
Severe (≥24)	81 (76)	79 (74)	160 (75)
Baseline CGI-S score, mean (SD)[d]	4.6 (0.6)	4.6 (0.6)	4.6 (0.6)
Past psychedelic use, n (%)			
Any psychedelic[e]	18 (17)	27 (25)	45 (21)
LSD	10 (9)	9 (8)	19 (9)
Number of past GAD medications, n (%)			
0	35 (33)	36 (34)	71 (33)
1	31 (29)	34 (32)	65 (30)
≥2	41 (38)	37 (35)	78 (36)
Comorbid MDD, n (%)	43 (40)	37 (35)	80 (37)
Years since GAD diagnosis, mean (SD)	11.1 (10.1)	12.9 (11.6)	12.0 (10.9)
Years since onset of GAD symptoms, mean (SD)	21.9 (13.7)	25.7 (14.4)	23.8 (14.1)

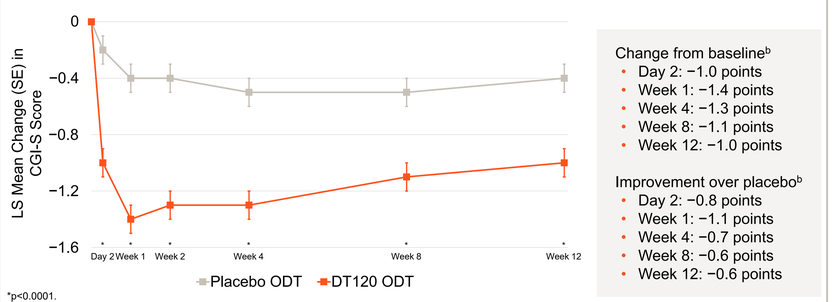
[a]Based on ITT population.
[b]The HAM-A is a 14-item clinician-rated outcome measure assessing various domains of anxiety with a range of 0–56. In Voyage, HAM-A ratings were assessed by central raters blinded to both treatment assignment and visit number.
[c]Eligibility criteria required a baseline HAM-A score of ≥20; moderate symptoms are defined as a HAM-A score of 16–23.
[d]The CGI-S is a clinician-rated outcome measure assessing overall severity of illness with a range of 1 to 7.
[e]Psychedelics include LSD, psilocybin, dimethyltryptamine, and other classic serotonergic psychedelics.
CGI-S, Clinical Global Impressions–Severity; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; ITT, intention-to-treat; LSD, lysergic acid diethylamide; MDD, major depressive disorder; ODT, orally disintegrating tablet; SD, standard deviation.

Figure 2. HAM-A Change From Baseline Through Week 12[a,b]



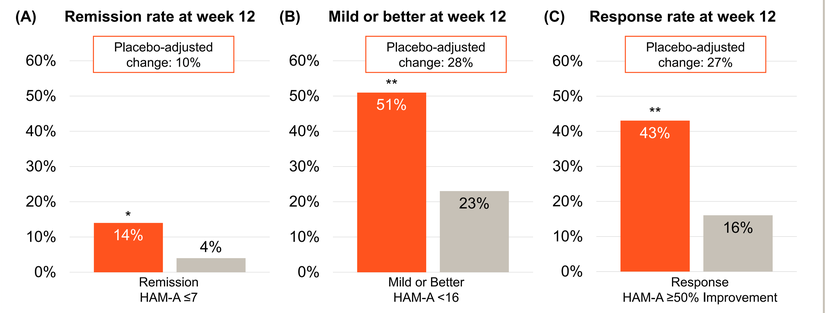
*p<0.0001.
[a]ITT population.
[b]Primary endpoint of the study was change from baseline in HAM-A at week 12 using a mixed-effects model repeated-measures statistical analysis with reference-based imputation.
ITT, intention-to-treat; HAM-A, Hamilton Anxiety Rating Scale; LS, least squares; ODT, orally disintegrating tablet; SE, standard error.

Figure 3. CGI-S Change From Baseline Through Week 12[a,b]



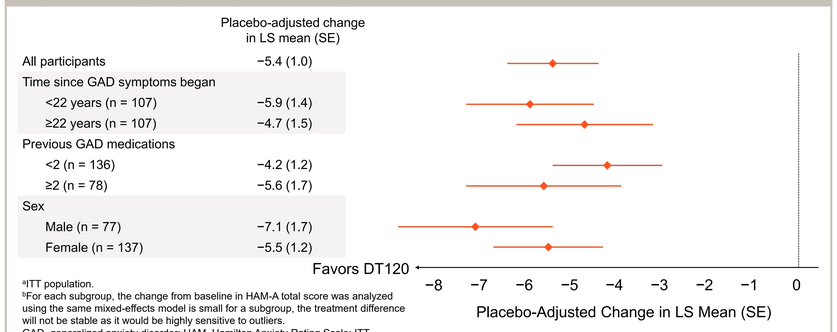
*p<0.0001.
[a]ITT population.
[b]Key secondary endpoints of the study were change from baseline in CGI-S at day 2 and week 1 using a mixed-effects model repeated-measures statistical analysis with reference-based imputation.
CGI-S, Clinical Global Impressions–Severity; ITT, intention-to-treat; LS, least squares; ODT, orally disintegrating tablet; SE, standard error.

Figure 4. HAM-A (A) Remission, (B) Mild or Better, and (C) Response Rates at Week 12[a]



*p<0.05; **p<0.0001.
[a]ITT population.
HAM-A, Hamilton Anxiety Rating Scale; ITT, intention-to-treat; ODT, orally disintegrating tablet.

Figure 5. Subgroup Analysis of Change in HAM-A Score From Baseline at Week 12[a,b]



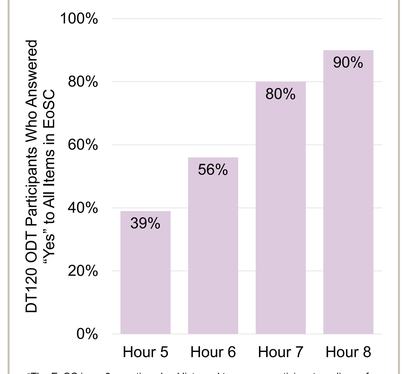
[a]ITT population.
[b]For each subgroup, the change from baseline in HAM-A total score was analyzed using the same mixed-effects model is small for a subgroup, the treatment difference will not be stable as it would be highly sensitive to outliers.
GAD, generalized anxiety disorder; HAM, Hamilton Anxiety Rating Scale; ITT, intention-to-treat; LS, least squares; SE, standard error.

Table 2. Summary of AEs Reported During Part A of the Voyage Study[a,b]

AE	DT120 ODT n = 107	Placebo ODT n = 107
Any TEAE, n (%)	106 (99)	74 (69)
Mild	65 (61)	49 (46)
Moderate	41 (38)	24 (22)
Severe	0	1 (1)[c]
Any study drug–related TEAE, n (%)	102 (95)	51 (48)
Any AESI, n (%)	100 (93)	30 (28)
Any treatment-emergent SAE, n (%)	0	3 (3)
Any TEAE leading to discontinuation, n (%)	1 (1)[d]	0
Any TEAE leading to death, n (%)	0	0

[a]Safety population in study Part A.
[b]AEs were collected in accordance with FDA final guidance for psychedelic drug development, which includes expected effects characterized as positive, favorable, or neutral.
[c]Severe AE was diverticulitis, occurring approximately 9 weeks after dose.
[d]Participant discontinued due to recurrence of depression approximately 6 weeks after dose.
AE, adverse event; AESI, AE of special interest; FDA, United States Food and Drug Administration; ODT, orally disintegrating tablet; SAE, serious AE; TEAE, treatment-emergent AE.

Figure 6. Time to EoSC Clearance[a]



[a]The EoSC is an 8-question checklist used to assess participant readiness for completion of monitoring after receiving DT120.
ODT, orally disintegrating tablet; EoSC, End-of-Session Checklist.

Conclusions

- Significant improvements in HAM-A total score were observed by week 1 and sustained through week 12
- CGI-S scores significantly improved at all time points
- DT120 demonstrated a favorable safety profile, with no serious AEs
- These findings following a single administration of DT120 support its continued development as a potential treatment option for patients with GAD

References

1. Wittchen H, et al. *J Clin Psychiatry.* 2001;62:15-21. 2. Ringeisen H, et al. RTI International; 2023. Accessed August 13, 2026. https://www.rti.org/publication/mental-substance-use-disorders-prevalence-study-findings-report 3. World Health Organization. Accessed August 13, 2026. https://www.who.int/news-room/fact-sheets/detail/anxiety-disorders 4. Ruscio A, et al. *JAMA Psychiatry.* 2017;74(5):465-75. 5. Ansara E. *Ment Health Clin.* 2020;10(6):326-34. 6. Bandelow B, et al. *Dialogues Clin Neurosci.* 2017;19(2):93-107. 7. Robison R, et al. *JAMA.* 2025;334(15):1358-72.

Acknowledgments

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Disclosures

PDT holds a passive equity interest in Definium Therapeutics, Inc., AtaiBeckley, and Helus Pharmaceuticals, and has served on paid Advisory Committees for AtaiBeckley and Helus Pharmaceuticals. PLJ, TMS, JJ, SMK, MC, JMF, CC, RB, and DRK are employees of Definium Therapeutics, Inc.

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